Remarks

The Office action mailed September 22, 2008, has been reviewed and carefully considered. Claims 26, 29, 41-45, 55, 56, 58 and 59 have been amended. Claim 60 is new. Support for these amendments and newly added claim 60 can be found throughout the specification including page 14, line 1 – page 15, line 5 and the claims as originally filed. No new matter has been added. Following entry of these amendments, claims 26-29, 36 and 41-60 are pending, claims 47-54 being withdrawn.

35 U.S.C. §103 Rejections

Claims 26-29, 36, 41-46 and 55-59 stand rejected as allegedly obviousness under 35 U.S.C. §103(a) over Simon *et al.* (*AIDS Res. And Hum. Retroviruses*, 17(10):937-952, 2001) combined with Tam (*PNAS*, 85(15): 5409-5413, 1988), Guertler *et al.* (U.S. Patent No. 6,566,513) and Kim *et al.* (*J. Immunol. Meth.* 257:51-54, 2001). Applicants respectfully traverse this rejection for at least the following reasons.

To establish a *prima facie* case of obviousness, the Office must establish that (1) the references teach or suggest all claim limitations; (2) there is some suggestion or motivation to combine the references, either in the references or in common general knowledge of one of skill in the art; and (3) there is a reasonable expectation of success (MPEP § 2143). The Office has failed to establish a *prima facie* case of obviousness for the presently pending claims, as described in detail below, at least because Simon *et al.* combined with the secondary references do not (1) teach or suggest all claim limitations, (2) fail to provide motivation to combine the references, and (3) there was not a reasonable expectation of success.

Independent Claims 26 and 29

Cited references fail to teach, suggest or disclose all claim limitations

Simon *et al.* describe the use of synthetic linear peptides directed at the gp41/36 and V3 regions of various lentivirus lineages in order to detect and differentiate the various lineages in human and non-human serum samples. The exemplified gp41/36 peptides disclosed in Simon *et al.* have 24 residues and the exemplified V3 residues have between 25-27 residues and are coated directly onto the walls of microtiter plates in the described immunoassays. As correctly noted in the September 22,

2008 Office action (page 6, item 13), Simon *et al.* do not teach multiple antigenic peptides (MAP) or peptide sequences of less than 16 amino acid residues. In particular, no where do Simon *et al.* teach, suggest or disclose an enzyme immunoassay construct that includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" as currently claimed.

The importance of these features is explained in the present specification at page 14, line 5 – page 15, line 17. First, the "d-aspartic acid residue improves the solubility of the MAP" (page 14, lines 9-10)." Further, the plurality of shorter linear peptides in the presently disclosed MAPs enables optimization for specificity and sensitivity – "the "specificity is enhanced by shorter linear peptide portions that are more antigenicity focused and the sensitivity is enhanced by the plurality of shorter linear peptides" (page 15, lines 6-12). For example, "the analytical discernability of the assay results is increased (*e.g.*, the optical density readout exhibits a more intense color)" (page 15, lines 12-13).

Therefore, Simon *et al.* fail to teach, suggest or disclose all of claim limitations of the presently pending claims.

Additionally, Tam, Guertler *et al.* and Kim *et al.* (hereinafter referred collectively as secondary references) either alone or in combination do not teach, suggest or disclose all of the claim limitations as required to establish a *prima facie* case of obviousness.

Guertler *et al.* relates to the immunodeficiency virus SIM27 of drill monkeys. Although Guertler *et al.* disclose a 32-mer peptide SEQ ID NO: 31 derived from the cysteine loop region of gp41/gp36 of SIV-CPV that includes 11 amino acids of disclosed peptide SEQ ID NO: 1, nowhere do

Guertler *et al.* teach, suggest or disclose an enzyme immunoassay construct that includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" as currently claimed.

Tam discloses several MAP constructs using various antigenic peptides (see Table I). However, none of the antigenic peptides are present in, derived from, or related to, a primate immunodeficiency virus. Moreover, Tam explored utilizing the MAP constructs for vaccines. There is no mention in Tam that MAP constructs could be utilized for diagnostic purposes, much less an enzyme immunoassay. Further, nowhere does Tam teach, suggest or disclose an enzyme immunoassay construct that includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" as currently claimed.

Kim *et al.* disclose the use of tandem repeats or multiple antigenic peptides as antigens to detect antibodies in immunoassays. Kim *et al.* employ a 13 residue HIV-1 peptide antigen in various formats to detect HIV-1 antibodies. However, nowhere do Kim *et al.* teach, suggest or disclose an enzyme immunoassay construct that includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues

and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" as currently claimed.

All of the structural features and properties of the claimed enzyme immunoassay construct have not been taught or suggested by the cited references. As such, it would not have been obvious to one of skill in the art to make the claim assay and the MAPs used within the assay. Therefore, a *prima facie* case of obviousness has failed to be established because the cited references either alone or in combination fail to teach all of the claim limitations of the presently pending claims.

Cited references fail to provide suggestion or motivation to combine the references

The present enzyme immunoassay construct includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix." None of the cited references provide suggestion or motivation to combine the references to arrive at the presently claimed invention.

As previously stated in the response to Office action submitted on January 13, 2009, one of ordinary skill in the art would not attempt to modify the assays set out in Simon *et al.* in accordance with any of the cited secondary references. First, the assay described in Simon *et al.* is reported to be both highly specific and sensitive. Page 949, col. 1 states:

> The use of different gp41/36 peptides allowed us to identify all the positive samples in the reference human panel. None of the HIV-1/HIV-2-negative samples included in the reference panel reacted with any of the peptides included in our test. In the filed evaluation panels, the sensitivity of the gp41/36 peptide array, which was used as the detection component, was excellent: all the WB positive samples were detected by the gp41/36 component (100% sensitivity and 98% positive predictive value).

Therefore, the assays described in Simon *et al.* are sensitive enough to detect anti-lentivirus antibodies when they are present in both reference and filed samples and do not produce false negative results. It is abundantly clear that these assays do not suffer from the sensitivity problem which might be remedied by solutions proposed in Tam or Kim *et al.* As such, the skilled person would have no reason to modify the assay of Simon *et al.*

Even if, for some reason, the skilled person were to attempt to modify the assay of Simon *et al.* in light of the cited secondary references, the result would not be the subject-matter of the present claims. The skilled person would not contemplate reducing the size of the peptides of Simon *et al.* because there is nothing in any of the cited references which might suggest that smaller peptides could effectively detect and differentiate isolates from different primate immunodeficiency virus (PIV) lineages. First, there is nothing in Simon *et al.* which might suggest to a skilled person the possibility that the gp41/35 and V3 peptides described might be reduced in length without compromising specificity or sensitivity. Second, there is nothing in any of the secondary references to suggest the formation of MAPs as presently claimed.

Although Guertler *et al.* disclose a 32-mer peptide SEQ ID NO: 31 derived from the cysteine loop region of gp41/gp36 of SIV-CPV that includes 11 amino acids of disclosed peptide SEQ ID NO: 1, nowhere do Guertler *et al.* suggest a MAP format or that antigenic peptides with sequences including less than 16 amino acid residues could effectively detect and differentiate isolates from different PIV lineages. Second, while Tam discloses several MAP constructs using various antigenic peptides (see Table I), none of the antigenic peptides are present in, derived from, or related to, a primate immunodeficiency virus. Further, even if Tam discloses a MAP system as asserted by the

Office on page 4 of the Office action, Tam does not teach or suggest a MAP construct as currently claimed (*e.g.*, a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix"). Finally, Kim *et al.* disclose the use of tandem repeats or multiple antigenic peptides as antigens to detect antibodies in immunoassays. Again, however, none of the MAP constructs include features of those presently claimed.

The skilled person would therefore at best reformat the peptides of Simon *et al.* in a tandem repeat or MAP format and the result would be tandem repeats or MAPs comprising gp41/36 peptides of 24 residues and V3 peptides of 25-27 residues. The skilled person would not employ a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" as presently claimed. As such, a *prima facie* case of obviousness has failed to be established because the cited references do not provide the motivation or suggestion to combine the references to arrive at the present invention and even if they did, they do not result in the invention as presently claimed.

One of Skill in the Art Could Not Have Predicted That Prior Art Could Have Been Modified with Reasonable Expectation of Success

Absent Applicants' disclosure of an enzyme immunoassay construct that includes a plurality of detection MAPs that each "consists of a core matrix and at least two detection linear antigenic sequences bonded to the core matrix by β-alanine and d-aspartic acid, each linear detection antigenic sequence is less than 16 amino acid residues and the β-alanine and d-aspartic acid serving as spacer amino acids between each detection linear antigenic sequence" and a plurality of differentiation MAPs that each "consists of a core matrix and at least two linear antigenic sequences bonded to the core matrix by diaminopropionic acid, each differentiation linear antigenic sequence is less than 16 amino acid residues and diminopropionic acid serving as a spacer amino acid between each differentiation linear antigenic sequence and the core matrix" one of ordinary skill in the art would not reasonably believe that such MAPs could be utilized for diagnostic purposes, much less an enzyme immunoassay. Although Tam explored utilizing the MAP constructs for vaccines, there was no mention that MAP constructs could be used for diagnostic purposes, let alone an enzyme immunoassay. Vaccines and immunoassays are quite different; one is therapeutic; the other is diagnostic. A person of ordinary skill in the art could not have reasonably predicted that an approach taken for a vaccine could be successfully applied in an immunoassay. The lack of connection to Simon *et al.* or the presently claimed immunoassay is especially apparent from Tam's utter failure to even mention a PIV sequence or any applicability to PIV in general.

Additionally, the present enzyme immunoassay construct includes MAPs with specific features including linear antigenic sequences of less than 16 amino acid residues that are bonded to a core matrix by specific amino acids. The significance of these lengths and amino acids is discussed in detail above. There is neither teaching nor suggestion in any of the cited references that antigenic sequences with such features could be used to both detect different PIV strains and discriminate between them. Therefore, one of ordinary skill in the art could not have reasonably predicted that such MAPs could be used to effectively detect and differentiate isolates from different PIV lineages.

Claims Dependent from Claim 26 or Claim 29

Claims 41-44, 55, 56 and 58 include antigenic peptides with specific amino acid sequences. None of the cited references teach, suggest or disclose these exact peptide sequences. As such, a *prima facie* case of obviousness has not been established with respect to these claims for not only the reasons

stated above for claims 26 and 29, but for failure of any of the cited references to teach or suggest (alone or in combination) the specific antigenic peptides as presently claimed.

Because the cited references fail to teach or suggest (alone or in combination) all of the elements of the claims, fail to provide motivation to combine the references, and there was not a reasonable expectation of success, a *prima facie* case of obviousness has not been established. Applicants respectfully request that the pending 35 U.S.C. §103(a) rejection be withdrawn.

Newly Added Claim 60

Newly added claim 60 is believed to be allowable for being free of the cited art and satisfying all conditions for patentability for at least all of the reasons set forth above for all of the presently pending claims.

Request for Rejoinder

Applicants thank the Examiner for recognizing that claims 26 and 29 are generic claims (Restriction Requirement, January 31, 2007). Thus, Applicants request that withdrawn claims 47-54 be rejoined as provided by 37 CFR 1.141.

Conclusion

It is respectfully submitted that the application is in condition for allowance. Should there be any questions regarding this application, Examiner Peng is invited to contact the undersigned attorney at the telephone number shown below.

Respectfully submitted,

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